UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Kulkowsky, P. Art Unit: 1615

Re: Application of: **Martinez, Anthony J.**, et al.

Serial No.: 09/293,624

Filed: April 16, 1999

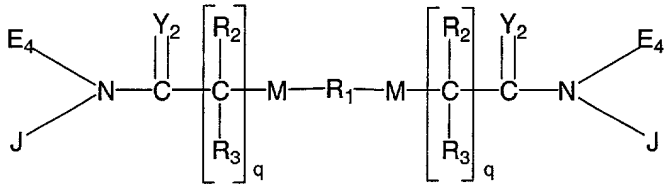
For: **TERMINALLY-BRANCHED POLYMERIC LINKER AND POLYMERIC CONJUGATES CONTAINING THE SAME**

Version with markings to show changes made

IN THE CLAIMS:

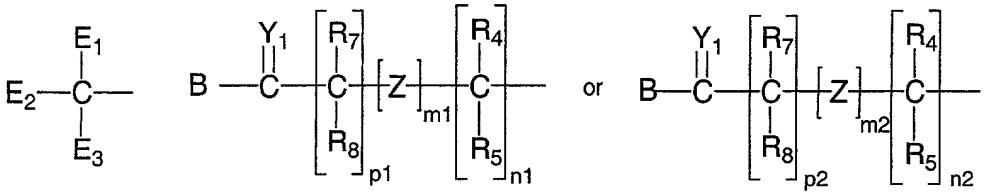
Claim 1 has been amended as follows:

1. (Thrice Amended) A compound comprising the formula:

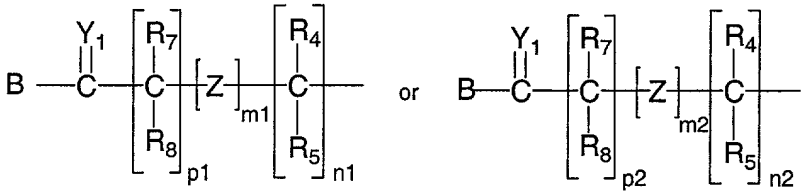


wherein:

J is

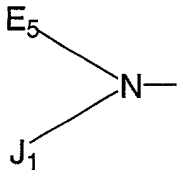


E_{1-4} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, C_{1-6} heteroalkoxy, and at least one of E_{1-4} is



wherein B is a leaving group, OH, a residue of a hydroxyl-containing moiety, a residue of

an amine-containing moiety or



wherein J_1 is the same as J, or another member of the group defining J and E_5 is the same as E_{1-4}, or another member of the group defining E_{1-4};

Y_{1-2} are independently O, S or NR_9;

M is a heteroatom selected from either X or Q; wherein X is an electron withdrawing group and Q is a moiety containing a free electron pair positioned three to six atoms from $C(=Y_2)$;

R_{2-5} and R_{7-9} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} ~~heteroakoxy~~ heteroalkoxy;

(m1) and (m2) are independently zero or one;

(n1), (n2), (p1), (p2) and (q) are independently zero or a positive integer;

Z is an electron withdrawing group; and

R_1 is a polymeric residue of a substantially non-antigenic polymer having a molecular weight of at least about 20,000 Daltons.

Claim 16 has been amended as follows:

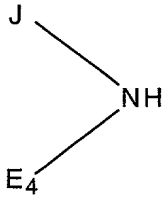
16. (Amended) The compound of claim 1, wherein B is a residue of a member of the group consisting of Ara-C, camptothecin, camptothecin analogs, paclitaxel, taxoteres, gemcitabine, podophyllotoxin, fluconazole, ciclopirox, amphoteracin B, nystatin, doxorubicin, daunorubicin, maytansine, vancomycin and erythromycin.

Claim 20 has been amended as follows:

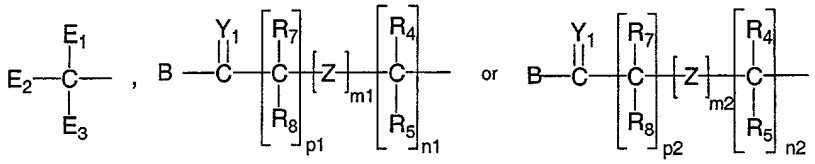
20. (Amended) A method of preparing a polymeric transport system, comprising

a) reacting a compound of formula:

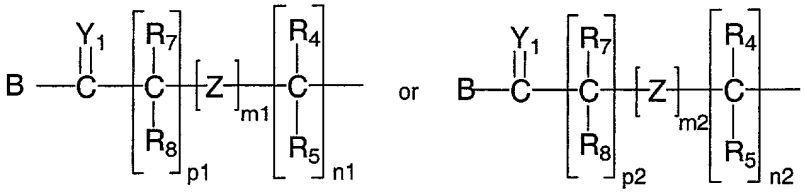
(IXb1)



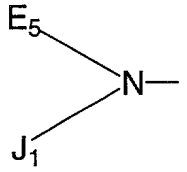
wherein J is:



E_{1-4} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~subsituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, C_{1-6} heteroalkoxy,



and at least one of E_{1-4} includes a B moiety, wherein B is a leaving group, OH or



wherein J_1 is the same as J, or another member of the group defining J and E_5 is the same as E_{1-4} or another member of the group defining E_{1-4};

Y_1 is O, S, or NR_9;

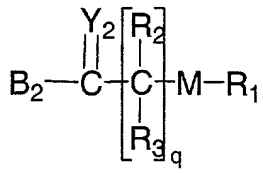
R_{4-5} and R_{7-9} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~subsituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

(m1) and (m2) are independently zero or one;

(n1), (n2), (p1), and (p2) are independently zero or a positive integer; and

(Z) is an electron withdrawing group;

with a compound of the formula:

(X) 

wherein

B_2 is a leaving group which is capable of reacting with an unprotected amine;

Y_2 is O, S, or NR_9;

q is independently zero or a positive integer;

R_{2-3} are selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~substituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

M is a heteroatom selected from either X or Q; wherein X is an electron withdrawing group and Q is a moiety containing a free electron pair positioned three to six atoms from $C(=Y_2)$; and

(R_1) is a polymeric residue; and

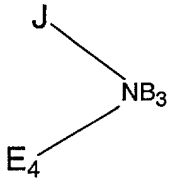
b) reacting the resultant compound with a sufficient amount of a biologically active moiety having a substitutable hydroxyl or amino group.

Claim 21 has been amended as follows:

21. (Amended) A method of preparing a polymeric transport system, comprising

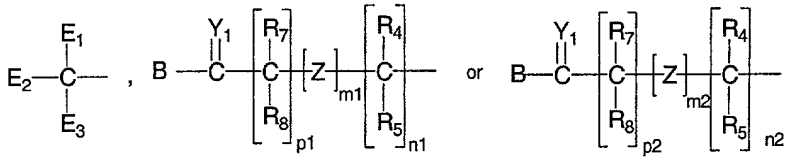
a) reacting a sufficient amount of a biologically active moiety having a substitutable hydroxyl or amino group with a compound of the formula:

(IX)



wherein B_3 is a cleavable protecting group;

J is:



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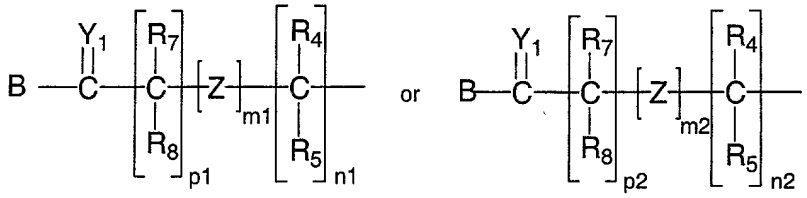
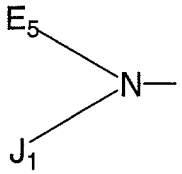


and at least one of E_{1-4} includes a B moiety, wherein B is a leaving group, OH, or



wherein J_1 is the same as J, or another member of the group defining J and E_5 is the same as E_{1-4} or another member of the group defining E_{1-4};

Y_1 is O, S, or NR_9;

R_{4-5} and R_{7-9} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~subsituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

(m1) and (m2) are independently zero or one;

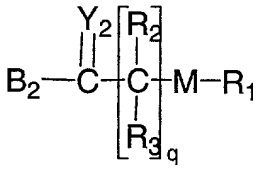
(n1), (n2), (p1), and (p2) are independently zero or a positive integer; and

(Z) is an electron withdrawing group;

with a biologically active moiety having a hydroxyl or amine group;

b) deprotecting the resultant intermediate by removing B_3; and

c) reacting the deprotected intermediate compound with a compound of the formula

(X) 

wherein

B_2 is a leaving group which is capable of reacting with an unprotected amine;

Y_2 is O, S, or NR_9;

q is independently zero or a positive integer;

R_{2-3} are selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~subsituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

M is a heteroatom selected from either X or Q; wherein X is an electron withdrawing group and Q is a moiety containing a free electron pair positioned three to six atoms from $C(=Y_2)$; and

(R_1) is a polymeric residue.

FIRST CLASS MAIL CERTIFICATION
I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the "Commissioner of Patents and Trademarks, Washington, D.C. 20231" on November 2, 2001.
ROBERTS & MERCANTI, L.L.P.

By:________________________
Sapna Gadhia

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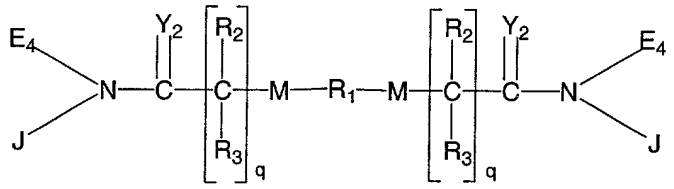

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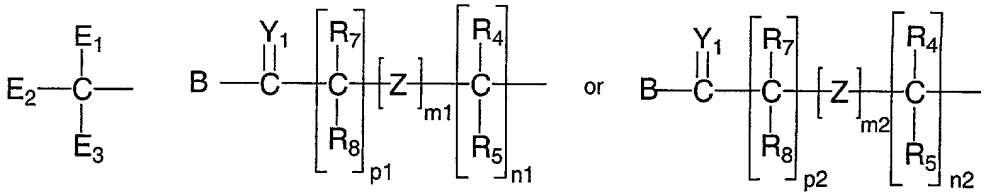

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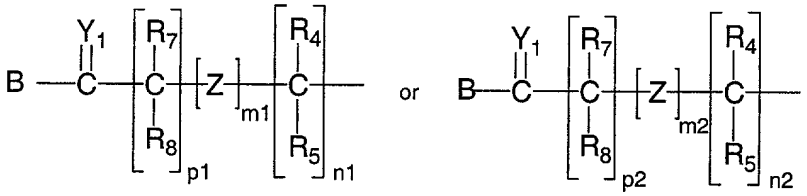
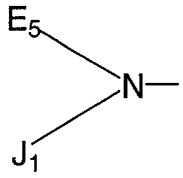


wherein B is a leaving group, OH, a residue of a hydroxyl-containing moiety, a residue of

an amine-containing moiety or



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(m1) and (m2) are independently zero or one;

(n1), (n2), (p1), (p2) and (q) are independently zero or a positive integer;

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R_1 is a polymeric residue of a substantially non-antigenic polymer having a molecular weight of at least about 20,000 Daltons.

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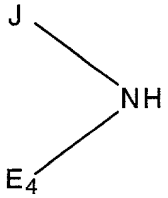
16. (Amended) The compound of claim 1, wherein B is a residue of a member of the group consisting of Ara-C, camptothecin, camptothecin analogs, paclitaxel, taxoteres, gemcitabine, podophyllotoxin, fluconazole, ciclopirox, amphoteracin B, nystatin, doxorubicin, daunorubicin, maytansine, vancomycin and erythromycin.

Claim 20 has been amended as follows:

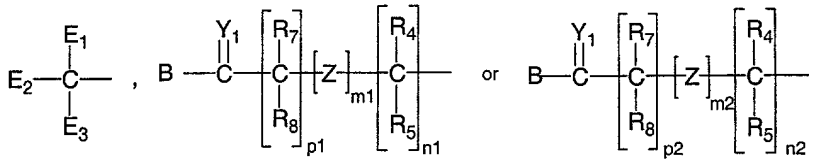
20. (Amended) A method of preparing a polymeric transport system, comprising

a) reacting a compound of formula:

(IXb1)



wherein J is:



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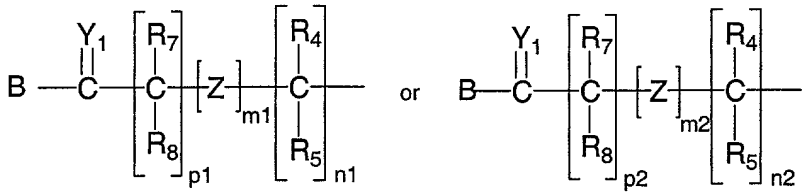
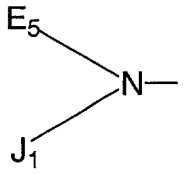


and at least one of E_{1-4} includes a B moiety, wherein B is a leaving group, OH or



wherein J_1 is the same as J, or another member of the group defining J and E_5 is the same as E_{1-4} or another member of the group defining E_{1-4};

Y_1 is O, S, or NR_9;

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(m1) and (m2) are independently zero or one;

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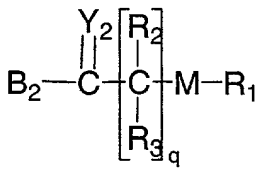
with a compound of the formula:

(X)



wherein

B_2 is a leaving group which is capable of reacting with an unprotected amine;

Y_2 is O, S, or NR_9;

q is independently zero or a positive integer;

R_{2-3} are selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~subsituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

M is a heteroatom selected from either X or Q; wherein X is an electron withdrawing group and Q is a moiety containing a free electron pair positioned three to six atoms from $C(=Y_2)$; and

(R_1) is a polymeric residue; and

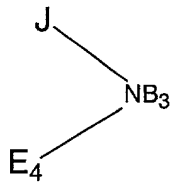
b) reacting the resultant compound with a sufficient amount of a biologically active moiety having a substitutable hydroxyl or amino group.

Claim 21 has been amended as follows:

21. (Amended) A method of preparing a polymeric transport system, comprising

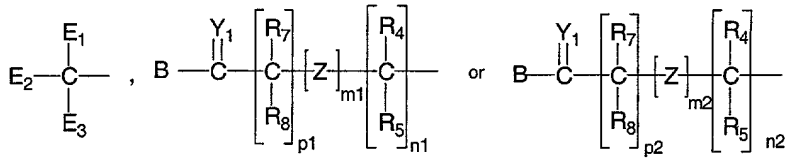
a) reacting a sufficient amount of a biologically active moiety having a substitutable hydroxyl or amino group with a compound of the formula:

(IX)



wherein B_3 is a cleavable protecting group;

J is:



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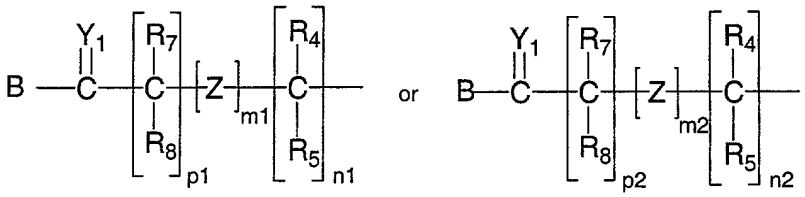

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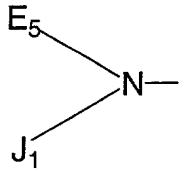

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(m1) and (m2) are independently zero or one;

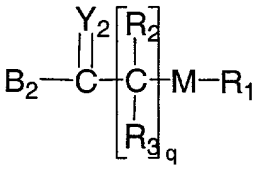
(n1), (n2), (p1), and (p2) are independently zero or a positive integer; and

(Z) is an electron withdrawing group;

with a biologically active moiety having a hydroxyl or amine group;

b) deprotecting the resultant intermediate by removing B_3; and

c) reacting the deprotected intermediate compound with a compound of the formula

(X) 

wherein

B_2 is a leaving group which is capable of reacting with an unprotected amine;

Y_2 is O, S, or NR_9;

q is independently zero or a positive integer;

R_{2-3} are selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, ~~subsituted C_{1-6} heteroalkyls,~~ substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

M is a heteroatom selected from either X or Q; wherein X is an electron withdrawing group and Q is a moiety containing a free electron pair positioned three to six atoms from $C(=Y_2)$; and

(R_1) is a polymeric residue.

FIRST CLASS MAIL CERTIFICATION
I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the "Commissioner of Patents and Trademarks, Washington, D.C. 20231" on November 2, 2001.
ROBERTS & MERCANTI, L.L.P.

By:_____
Sapna Gadhia

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